

## REMARKS/ARGUMENT

In the Office Action the Examiner raised a question concerning priority. It is respectfully noted that an ADS was filed in this case. Also, the PCT mentioned by the Examiner is this case and the present application is the National Stage (371 filing) of the PCT, so the PCT is NOT a related case within the meaning of 35 USC Sec. 120 or 37 C.F.R. 1.78

The Examiner's comment concerning the last IDS is noted and will be corrected, if necessary.

The comments in the Office Action respecting restriction are duly noted.

With respect to the claims, the claims have been amended according to the following.

Claim 1 has been amended by combining with claim 3.

Claims 2, 9, 13, 21, 24 and 27 have been amended as indicated therein. Support for the addition of "polyunsaturated fatty acids" may be found, inter alia, page 7 line 5; page 19, third full paragraph, last line; of the WO publication. That Omega-3 and Omega-6 lipids (lines 7-8, page 8 of the WO publication is well known to the man of skill in the art.

Support for the definition of the biofunctional ingredient in claim 24 may be found, inter alia, first paragraph, page 7 of the WO publication.

Claims 3, 4, 6, 7, 8, 10, 11, 12, 14, 15, 18, 22, 25, 28 and 39 have been amended.

Claims 33-35 have been amended. Support for the amendment may be found, inter alia, in the fourth full paragraph, page 21 of the WO publication.

New claim 45 has been added. Support for this claim may found, inter alia, in original claim 3.

New claim 46 has been added. Support for this claim may found, inter alia, in original claim 11.

New claims 47-48 have been added. Support for these claims may found, inter alia, in original claim 3.

New claim 49 has been added. Support for this claim may found, inter alia, in previous

claim 22.

New claim 50 has been added. Support for this claim may found, inter alia, in previous claim 28.

New claim 51 has been added. Support for this claim may found, inter alia, in claim 9.

New claim 52 has been added. Support for this claim may found, inter alia, in claim 13.

It is respectfully submitted that no new matter has been added during the process of amending the claims.

## Claims

### Claim Rejections - 35 USC § 112

The Examiner rejected Claims 33-34 based on 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. According to the Examiner, the specification by way of the prior art, while being enabling for enhancement of cognitive performance and learning ability and treating dementia, does not reasonably provide enablement for preventing memory loss. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

According to the Examiner, The specification, or the prior art, lack significant guidance from the specification or the prior art with regard to preventing memory loss utilizing the phosphatidylserine composition of matter, and this makes practicing the scope of the invention unpredictable. The Examiner maintains that the specification provides no direction or guidance for preventing memory loss. One of ordinary skill would undergo undue experimentation in deducing if the compositions can be utilized to prevent memory loss and then determine what sort of administration regimen can actually be utilized to prevent memory loss. This is particularly difficult in light of the state of the art's recognition which indicates that causes of dementia include head injury which is difficult to predict when that would occur. Furthermore in light of the state of the art's

recognition that age-related memory loss is diagnosed usually after signs of memory loss begin to appear and then treatment can only be utilized to suppress the decline of memory loss and not actually return memory function.

The Examiner further states that the working examples of the specification are directed towards formulating the compositions of the instant invention. However, the examples do not enable one to utilize the compositions to prevent memory loss.

The Examiner concludes that because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used to prevent memory loss as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention as claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

The Examiner noted that while intended uses are not given patentable weight, the enablement of compositions reciting activity or intended use must be considered.

Without conceding to the Examiner's rejection, in order to expedite examination these claims have been amended to recite use of the PS in improving memory loss. Support for the amendment may be found, e.g. in the 4<sup>th</sup> full paragraph, page 21 of the WO publication.

The Examiner rejected Claims 2, 9-22, 24-25, 27-28 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The Examiner maintains that these claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession

of the claimed invention.

According to the Examiner, the specification discloses chemicals, such as lecithin, phospholipids, vitamins, anti-oxidants, minerals, sterols, amino acids, poly-unsaturated fatty acids and carbohydrates which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, claim(s) 2, 9-22, 24-25, 27-28, is(are) directed to encompass functional ingredient, bio-functional ingredient, nutritional proteins or peptides, sterol derivatives, carbohydrate derivatives, plant extracts, fermentation products, glyceride derivatives, and active ingredient, which only correspond in some undefined way to specifically instantly disclosed chemicals. None of these derivatives, functional ingredients, bio-functional ingredients, proteins, peptides, extracts, fermentation products and active ingredients meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The instant specification provides no guidance as to what proteins, peptides, functional ingredients, fermentation products and active ingredients are contemplated as falling within the scope of the instant claims.

According to the Examiner, therefore, only the above chemically structurally defined chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant.

Without conceding to the Examiner's assertions, in order to expedite examination, the claims have been amended.

The Examiner rejected Claims 2-4, 6-17, 21-22, 24-25, 27-28, 30-35 and 42-44 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as follows:

Claims 3, 11, 22, 25 and 28 recite the broad recitation storage period of at least 6 months, and the claim also recite preferably at least 12 months and more preferably at least 24 months, which is the narrower statement of the range/limitation. In response, these claims have been amended.

Claim 4 recites the broad recitation phospholipase activity, and the claim also recites particularly phospholipase D activity, which is the narrower statement of the range/limitation. In response, this claim has been amended.

Claim 6 recites the broad recitation salt, and the claim also recites preferably the sodium salt, which is the narrower statement of the range/limitation. In response, this claim has been amended.

Claim 7 recites the broad recitation metal chelator, and the claim also recites preferably EDTA, which is the narrower statement of the range/limitation. In response, this claim has been amended.

Claim 8 recites the broad recitation salt, and the claim also recites preferably the calcium salt, which is the narrower statement of the range/limitation. In response, this claim has been amended.

Claim 9 recites the broad recitation form of a oil, and the claim also recites preferably a medium-chain triglyceride, which is the narrower statement of the range/limitation. In response, this claim has been amended.

Claim 10 recites the broad recitation about 1 to about 90% (w/w) phosphatidylserine, and the claim also recites preferably from about 2.5 to about 55 (w/w)%, which is the narrower statement of the range/limitation. In response, this claim has been amended.

Claims 12 and 16 recite the broad recitation biofunctional ingredient, and the claim also recites preferably at least one of lecithin, phospholipids ... , which is the narrower statement of the range/limitation. In response, these claims have been amended.

Claim 13 recites the broad recitation a liquid base, and the claim also recites preferably a lipid base and more preferably an oil base, which is the narrower statement of the range/limitation. In response, this claim has been amended.

Claim 14 recites the broad recitation from about 1 to about 70% (w/w), and the claim also recites preferably about 5 to 45% (w/w), which is the narrower statement of the range/limitation. In response, this claim has been amended.

Claim 15 recites the broad recitation triglyceride base, and the claim also recites particularly medium-chain triglyceride base or vegetable oil, which is the narrower statement of the range/limitation. In response, this claim has been amended.

Claims 33 and 34 recite the broad recitation memory loss, and the claim also recite particularly age-related memory loss, which is the narrower statement of the range/limitation. These claims have been amended, as referred to above.

Claims 2, 9, 13, 21, 24 and 27 it is contended as currently written are vague and indefinite. The claims recites the composition of matter preferably comprises from about 1 to about 99% (w/w) phosphatidylethanolamine. The presence of the word preferably results in the claim being indefinite because it is unclear if the phosphatidylethanolamine is required by the claims or only an optional component. In response, these claims have been amended.

Claims 2, 9, 13, 21, 24 and 27 it is contended as currently written are vague and indefinite. The claims recite omega-3 source and omega-6 source. However, neither the instant claim nor the instant specification indicates what this source is or what Omega-3

or Omega-6 is referring to. Is it particular fatty acids or particular lipids? Furthermore it is unclear if only the source has to be present in an amount from about 1 to about 99% or if the Omega-3 or Omega-6 chemical needs to be present in this amount. In response, these claims have been amended to recite "polyunsaturated fatty acids".

Claims 2, 9, 13, 21, 24 and 27 as currently written are contended to be vague and indefinite because the claims recite the composition of matter comprises other functional ingredients. It is further contended that neither the instant claims nor the instant specification indicates what is meant by the term "other functional ingredients" or what types of ingredients would be considered "other functional ingredients". Thus, it is contended that the resulting claim does not clearly set forth the metes and bounds of the patent protection desired for other functional ingredients. In response, these claims have been amended.

The term "substantially soluble" in claim 6 is a relative term which it is contended renders the claim indefinite because the term "substantially soluble" is not defined by the claim, and thus the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In response, this claim has been amended.

The term "substantially non-soluble" in claim 8 is a relative term which it is contended renders the claim indefinite because the term "substantially soluble" is not defined by the claim, and thus the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In response, this claim has been amended.

Claims 12 and 16 it is contended as currently written are vague and indefinite because the claims recite nutritional carbohydrates, and therefore, neither the instant claims nor the instant specification indicates what these nutritional carbohydrates are.

Furthermore, it is contended that no guidance is given as to differentiate nutritional carbohydrates over other types of carbohydrates, and that the resulting claim does not

clearly set forth the metes and bounds of the patent protection desired for nutritional carbohydrates. Applicant respectfully submits that the term "nutritional carbohydrates" is clear to the man of skill in the art. Nonetheless, without conceding to the Examiner's objections, these claims have been amended.

Claims 9 and 13 it is contended as currently written are vague and indefinite because Claim 13 recites a dispersion of phosphatidyl serine and that the phosphatidylserine appears to be the same as that claimed in claim 9 in which the phosphatidylserine is dissolved in oil. Thus, it is contended that Claim 13 recites dispersing the same phosphatidylserine in the same oil as the phosphatidylserine is dissolved and therefore, it is unclear how the same phosphatidylserine can both be dispersed and dissolved. Further it is contended that claim 13 does not recite that the phosphatidylserine is a salt thereof. In response, claims 9 and 13 have been amended to recite that the phosphatidylserine is in the form of a soluble, respectively non-soluble salt. Support for this amendment may be found, for example, in claims 6, respectively 8.

#### Claim Rejections - 35 USC § 102

The Examiner stated that the instant application claims a composition of matter comprising from about 1 to about 99% (w/w) phosphatidylserine.

The Examiner rejected Claims 1, 3-8, 18 and 42-44 under 35 U.S.C. 102(b) as being anticipated by Buchholz et al. (US Patent No. 6514973, cited on PTO Form 1449). According to the Examiner, Buchholz et al. exemplify a composition consisting of phosphatidylserine, choline, S-adenosyl methionine, serine, and L-5-methyltetrahydrofolic acid. The amount of phosphatidylserine is 9% based on the total weight of the composition. The Examiner contends that it is taught that component A is phosphatidylserine and their physiologically acceptable salts (column 4, lines 37-40), and that in his view, physiologically acceptable salts include sodium, potassium, magnesium, calcium, ammonium and substituted ammonium salts (column 5, lines 17-



24). The disclosure is clear that Buchholz et al. does not exemplify the salt form of the phosphatidylserine. Therefore are only two choices for the phosphatidylserine, the free base or the salt form. According to the Examiner, therefore, one of ordinary skill in the art would immediately envision utilizing the salt form of the phosphatidylserine.

Applicant respectfully traverses for the following reasons.

Claims 1 has been amended to define the storage stability of the PS composition, namely: "no more than about 1 to about 5% of the phosphatidylserine are decomposed after a storage period of at least 6 months". The same storage stability is defined for claim 18, which depends from amended claim 13. The Examiner's attention is also drawn to the storage stabilities defined in claims 3 (at least 12 months) and 45 (at least 24 months), and correspondingly 46-50.

As explained in the specification (see, e.g. page 2, last paragraph), one of the main problems associated with PS preparations, especially in liquid form, is their low stability, due to rapid decomposition. The rapid decomposition changes the structure of phosphatidyl serine (removes the serine head group,) causing loss of activity. The inventors succeeded in preparing storage stable PS compositions, which maintain at least 95% of the PS after long storage (see, by way of example only, Table 4, page 33 - no loss of PS in liquid preparation after 4 months of storage).

Additional experimental results, showing the improved stability of the PS preparations of the invention, also compared to conventional preparations, are included in the attached Annex. These results clearly show the storage-stability of the claimed PS composition, considerably superior compared to the stability of known compositions, even such known compositions claimed to be storage-stable.

According to Buchholz et al., the PS used was a commercially available product (see Col. 7, lines 4-5). As described in the specification, before the application date, commercially available PS was manufactured using phospholipase D (PLD), and

preparations so prepared suffered from the lack of stability, as discussed above (see page 2 of the specification), lowering the concentration of PS over storage time. Since Buchholz et al. do not even mention stability, let alone a process for producing storage-stable PS preparations, and since it used commercially available PS preparations, i.e. unstable preparations (as the conventional PS preparations tested in the Annex), it is respectfully submitted that this document does not negate the novelty of amended claim 1.

Therefore, it is respectfully submitted that the composition of matter of claim 1 differs patentably from the PS preparations described in Buchholz et al., as can be readily determined by the man of skill in the art on basis of the teachings of the specification. The present specification provides various methods for determining the stability of the PS preparation, the amount of residual PLD (phospholipase D), which causes degradation, or for determining the amount of active PS. For example, in page 32, just below Table 3, it is described that: "Next, the inventors analyzed other PS preparations produced by different PS manufacturers. The inventors found that the residual enzymatic activity of PLD was considerably higher comparing to the residual enzymatic activity of PS prepared by the inventors. For example, one such "foreign" PS preparation exhibited 0.0242 and 0.0196 units/ml in two batches of similar grade PS preparations." Thus, the man of the art can determine by straight-forward methods the difference between the PS used in Buchholz et al., and those of the present invention as defined in the amended claims. Another indicator taught by the present application is the Peroxide Value (PV), since hyperoxidation is also a cause for low grade PS preparations (see page 40 of the application, and Table 7). This is also an available route for the man of skill in the art to differentiate the preparations of the invention from those of the prior art, including Buchholz et al.

It may be mentioned that Buchholz et al. addresses a completely different technical problem, providing compositions which comprise PS, methyl transporter and methyl donor, as detailed by the Examiner, useful in the treatment of neurological and

pathopsychological diseases. The present invention is directed at providing storage-stable PS preparations, in liquid, powder or dispersion forms.

It is therefore respectfully submitted that claims 1, 3-8, 18 and 42-44, as well as new claims 45-50, are novel in view of the cited references.

The Examiner contended with regard to claim 7, that the use of a metal chelator to form the sodium salt is a product by process. According to the Examiner, since the claim is directed to a sodium salt of phosphatidylserine and Buchholz et al. teach the sodium salt, the resulting product is the same.

Applicant respectfully traverses. Claim 7 depends from claim 1, and thus defines a composition of mater that is storage stable for at least 6 months, and is novel in view of Buchholz et al.

The Examiner stated that since the preamble of the claim recited the term stable, the recitation stable was not given patentable weight. The stability of the phosphatidylserine compositions of matter and products thereof is now defined as a characteristic feature, which is absent from the prior art.

The Examiner further states regarding the functional limitation of claims 4 and 42-44, that Buchholz et al. is silent as to the phospholipase activity, however, the composition comprises the same phosphatidylserine. The Examiner asserts that where the prior art discloses subject matter there is reason to believe that it inherently includes functions that are newly cited or identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on".

Applicant respectfully traverses.

The attached Annex shows that commercially available compositions, such as those used by Buchholz, do not possess storage stability of at least 6, or at least 12, or at least 24 months. Hence, they are novel and useful and unobvious over Buchholz. Furthermore, as shown in the application (page 32 of the WO publication), PS compositions commercially available at the date of the application, such as the preparations used by Buchholz et al., contained residual PLD activity much higher than any such activity in compositions of the invention as claimed.

Regarding claim 18, the Examiner objected that use as a dietary supplement is a recitation of an intended use, and that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. According to the Examiner, if the prior art structure is capable of performing the intended use, and then it meets the claim. According to the Examiner Buchholz et al. teach the composition is a tablet. Therefore, the prior art is capable of being able to perform the intended use.

Also with regard to this objection, it is respectfully submitted that since the subject matter of the claim differs from the disclosure of Buchholz et al., at least in terms of the storage stability, the objection is no longer relevant.

The Examiner rejected Claims 1, 3-5, 18 and 42-44 under 35 U.S.C. 102(b) as being anticipated by Kiliaan et al. (WO 01/84961). According to the Examiner, Kiliaan et al. exemplify preparations comprising phospholipids. Example 1 is a capsule comprising about 14% phosphatidylserine. Example 2 is a pudding comprising about 1% phosphatidylserine. Example 3 is a powdered concentration comprising about 1% phosphatidylserine.

The Examiner stated that regarding the preamble of the claim reciting the term stable, the recitation stable has not been given patentable weight because the recitation occurs in the preamble. According to the Examiner a preamble is generally not accorded any

patentable weight. According to the Examiner the claim recites only one component which is phosphatidylserine, which is found in the product of Kiliaan et al.

Applicant respectfully traverses.

The preparation of Kiliaan et al. consists of 3 types of constituents:

- a. Long chain polyunsaturated fatty acids;
- b. At least two different phospholipids chosen from PC, PI, PE, PS; and
- c. One of the following: folic acid, vitamin B12, vitamin B6, magnesium and zinc.

Regarding the phospholipids fraction the following is mentioned: "...Phospholipid fraction can also consist...of mixture of synthetic phospholipids..." (page 8, line 9). In Examples 1 and 2, the authors use PS (120 and 100 mg respectively) which they mention to be synthetic. There is no reference to the origin of the PS (Manufacturer) neither to its stability. For the reason detailed above with regard to Buchholz, it cannot be expected that the PS used in by Kiliaan et al. has an enhanced stability in comparison with the common commercial PS used at the time the present application was filed (described in the Annex). Specifically, there is no reference to a PS preparation devoid of the PLD activity, a stable liquid preparation, a stable PS dispersion, or any process that might result in a stable PS (as the PS of the invention).

Therefore, in view of the limitation of the storage stability of the claimed PS compositions of matter and preparations thereof, it is respectfully submitted that the invention is novel in view of Kiliaan et al.

Regarding the functional limitation of claims 4 and 42-44, the Examiner stated that Kiliaan et al. is silent as to the phospholipase activity, however, the composition comprises the same phosphatidylserine, and therefore the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on". Also with regard to this objection, it is respectfully submitted

that since the subject matter of the claim differs from the disclosure of Kiliaan et al., at least in terms of the storage stability, the objection is no longer relevant.

The Examiner rejected Claims 1, 3-5, 18 and 42-44 under 35 U.S.C. 102(b) as being anticipated by Hensley et al. (WO 01/82902). The Examiner maintains that Hensley et al. exemplify preparations comprising mixed membrane phospholipids, see Example 1 a composition comprising one or more phospholipids selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinositol; the exemplified amounts of the phospholipids is from 87-96%.

Also in respect of Hensley et al., the Examiner states that regarding the preamble of the claim reciting the term stable, the recitation stable has not been given patentable weight because the recitation occurs in the preamble.

Applicant respectfully traverses.

Hensley et al. deals with phospholipid compositions for administering a drug or a biologically active molecule via the nasal mucosal membrane. The composition comprises of phospholipid carrier, a drug or a biologically active molecule. The phospholipid carrier comprises of one or more phospholipids selected from the group consisting of: phosphatidylcholine, phosphatidyl-ethanolamine, phosphatidylserine or phosphatidylinositol. Nothing is mentioned about the source of the PS (natural, synthetic, etc.), manufacturer, let alone the stability of the phospholipid preparations used. There should not be any reason to expect or believe that the PS used by Hensley et al. has an enhanced storage stability in comparison with the common commercial PS used at the time the application was filed (shown in the Annex). The arguments present above in respect of Buchholz et al. also apply to Hensley et al.

There is no reference to a PS preparation devoid of PLD activity, a stable liquid preparation, a stable PS dispersion, or any process that might result in a stable PS (as the PS of the invention).

In view of the above, and particularly in view of the limitation of the minimal storage stability of the claimed composition of matter and preparations thereof, it is respectfully submitted that also Hensley et al. does not deprive the invention of novelty.

Regarding the functional limitation of claims 4 and 42-44, the Examiner confirms that Kiliaan et al. is silent as to the phospholipase activity, however, the composition comprises the same phosphatidylserine. However, the Examiner maintains, as above, that the burden of proof is shifted to the Applicant. Since this section of the Office Action refers to Hensley et al. and not to Kiliaan, it appears that the Examiner made a mistake. In any event, the issue of PLD presence has been referred to and answered above.

Regarding claim 18, the Examiner objects that use as a dietary supplement, nutraceutical food and/or drug additive is a recitation of an intended use, and that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. The Examiner holds that Hensley et al. teach the composition is for nasal administration, and therefore, the prior is capable of being able to perform the intended use.

It is respectfully submitted that the above arguments re Buchholz and Kiliaan apply also to Hensley et al.

#### Claim Rejections - 35 USC § 103

The Examiner rejected Claims 2, 21-22, 24-25, 27-28, 30 and 33 under 35 U.S.C. 103(a) as being unpatentable over Kiliaan et al. in view of Haynes et al. (US Patent No. 5015483).

The Examiner contends that instant application claims a composition comprising from about 1 to about 99% (w/w) phosphatidylserine, from about 1 to about 99% (w/w) other functional ingredients, from about 1 to about 99% (w/w) phosphatidylcholine, from about 1 to about 99% (w/w) phosphatidylethanolamine, from about 1 to about 99% (w/w) phosphatidylinositol, from about 1 to about 99% (w/w) Omega-3 source, from about 1 to about 99% (w/w) Omega-6 source and/or from about 1 to about 99% (w/w) sterol or sterol esters.

The Examiner asserts that Kiliaan et al. is directed to preparations for the prevention and/or treatment of vascular disorders, and teaches that it is known in the art that phosphatidylserine can be utilized for improving cerebation, in particular for the treatment of Parkinson's disease and dementia such as Alzheimer's disease. Additionally it is contended as known that compounds such as phosphoethanolamine are utilized for the treatment of Alzheimer's disease (page 5, lines 8-14). The disclosure of Kiliaan et al. comprises long chain polyunsaturated fatty acids, phospholipids which fraction contains at least two different phospholipids selected from the group consisting of phosphatidylserine, phosphatidylinositol, phosphatidylcholine and phosphatidylethanolamine and compounds which factor in methionine metabolism such as folic acid, vitamin 812, vitamin 86, magnesium, zinc (page 5, lines 23-31). The long chain fatty polyunsaturated fatty acids are preferably omega-3 and/or omega-6 fatty acids (column 6, lines 12-13). It was further contended that a mixture of omega-3 and omega-6 long chain polyunsaturated fatty acids should be included in a ratio of omega 3 to omega 6 of about 2.5 to 5.5 w/w. It is further contended that the disclosure showed exemplified formulations comprise phospholipids from egg which comprise DHA (an omega-3) and AA (an omega-6), phosphatidylcholine and phosphatidylethanolamine. The amount of phospholipids added from egg is 4 g which provides about 20 mg of DHA and 20 mg of AA and about 77% phosphatidylcholine and about 16% phosphatidylethanolamine. Also added to this compound is phosphatidylserine in 100 mg, encapsulated fish oil in 0.3 g which provides about 30 mg of DHA and 30 mg EPA



(an omega-3) and single cell oil which provides 25 mg of AA. This example (example 2) additionally comprises other vitamins and minerals. Other exemplified forms are a powder and a capsule.

The Examiner asserts that while Kiliaan et al. teach that the phospholipid fraction contains at least two different phospholipids selected from the group consisting of phosphatidylserine, phosphatidylinositol, phosphatidylcholine and phosphatidylethanolamine and exemplifies formulations comprising three different phospholipids. Kiliaan et al. do not exemplify formulations comprising all four phospholipids.

The Examiner further asserts that Kiliaan et al. do not teach incorporating sterol or sterol esters. However, this deficiency is cured by Haynes et al.

It is contended that Haynes et al. teach liposome compositions for the stabilization of oxidizable substances, and the compositions comprise phospholipids and omega-3 and omega-6 fatty acids (column 5, lines 39-41). It is further contended as taught that cholesterol is known to be a stabilizer of phospholipids (column 2, lines 51-55), and that in compositions comprising phospholipids other lipids such as sterols and cholesterol can be added in order to reduce the permeability, strengthen the vesicle wall and generally improve the physical characteristics of a resulting liposome (column 10, lines 5-11). The amount utilized, as disclosed, will vary but generally not exceed a 1:1 ratio with the selected phospholipid (column 10, lines 15-17).

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Kiliaan et al. and Haynes et al. and utilize phosphatidylserine, phosphatidylcholine, phosphatidylethanolamine, and phosphatidylinositol, and that one of ordinary skill in the art would have been motivated to utilize all four phospholipids as Kiliaan et al. teach utilizing two or more of these four phospholipids and exemplify formulations comprising

three of the four phospholipids. Further it is contended that it would have been obvious to one of ordinary skill in the art to utilize all four phospholipids as they are all taught as being suitable, mixtures are taught as suitable, mixtures of three of more are exemplified and they are all taught as being utilized for the same purpose, particularly exemplified is a combination of phosphatidylcholine, phosphatidyl-ethanolamine, phosphatidylinositol for the improvement of vasoendothelial function. It would have been obvious to one of ordinary skill in the art to add phosphatidylserine as it is taught for being useful for treating dementia. Therefore, it would have been obvious to one of ordinary skill in the art to add phosphatidylserine for the added benefit of treatment dementia as taught by Kiliaan et al. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Kiliaan et al. and Haynes et al. and utilize sterol in the composition. One of ordinary skill in the art would have been motivated to add a sterol in order to improve the stability of the lipids as taught by Haynes et al.

Applicant respectfully traverses. The main technical problem addressed by the present invention is to provide storage stable phosphatidylserine compositions of matter, with minimal storage stability of 6 months. Kiliaan is completely silent as to the source, method of preparation, and the storage stability of the PS preparations to be used in their compositions. The technical problem addressed by Kiliaan et al. is to provide a composition for the treatment of cardiovascular disorders and not to stabilize PS compositions.

Haynes et al. relates to shelf-stable, edible liposome composition that contains polar lipids, edible unsaturated oil (like fish oil) and an aqueous medium. Phosphatidylserine (PS) is one of the options for the polar lipid fraction. It is claimed that this composition protects the fish oil from oxidation. The type of the PS is not mentioned. PS is not mentioned in any of the examples, rather it is mentioned only as an item on a list of possible polar lipids.

The stability of the composition is discussed in connection with stabilization of oxidizable unsaturated lipophilic compounds by the encapsulation of the material in the lipidic layer of a liposome to retard or inhibit oxidation. There is no indication of a possible enhanced stability of the PS itself or any process that can result in a stable form of PS. This document does not refer to stabilization of the PS, but to stabilization of the fish oil entrapped in the liposomes that are formed due to the presence of the polar solvent. To deduce from this that the PS, used only as a constituent of the liposome, is more stable than the common commercial PS used at the time the invention was filed, is, to say the least, far fetched.

Specifically, there is no reference to a PS preparation devoid of the PLD activity, a stable liquid preparation, or a stable PS dispersion, or any process that might result in a stable PS per se (as the PS of the invention).

The technical problem addressed by Haynes et al. is thus to prepare stable liposomes, that would protect fish oil contained in them from oxidation.

There would have been no motivation for the man of skill in the art to combine the teachings of Haynes with those of Kiliaan, i.e. to add sterols to the composition of Kiliaan. Even if combined, the result would not be stable PS compositions, as in the present application, that are storage stable for at least 6, or at least 12, or at least 24 months. The basis for the Examiner's assertion that the addition of sterol to the composition of Kiliaan would increase the stability of the PS in the product is unclear. Since the compositions of Kiliaan do not contain polar solvent, particularly water, no liposomes will form. The sterol (as mentioned by Haynes) does not protect the PS, rather, together with the PS it should form stable liposomes in order to protect the liposome content from oxidation. Liposomes are not part of the present invention scope. Therefore, the rejection is not founded. It should also be mentioned that stabilization of the PS per se, is definitely not the reason for the addition of sterol to the compositions of

the present invention, where the sterol is added as a functional ingredient, not as a stabilizer, because it is not a stabilizer.

It is therefore respectfully submitted that the invention as claimed is not obvious over Kiliaan et al., in view of Haynes et al.

The Examiner also stated that regarding the claimed amounts, the art teaches that the daily intake should be at least 200 mg of phospholipids, 120 mg long chain polyunsaturated fatty acids, at least 200 micrograms of folic acid and at least 0.5 g of citrate (page 11, lines 8-14). This equates to a phospholipid amount of about 24% and a long chain polyunsaturated amount of about 15%. It is taught that for best results the ratio of phosphatidylcholine and/or phosphatidylethanolamine to phosphatidylserine and/or phosphatidyl inositol is 0.5 to 20 (w/w) (page 7, lines 18-20). The ratio of omega-3 to omega-6 is about 2.5 to 5.5 (w/w). Haynes et al. teach that the amount of sterol will generally not exceed a 1:1 ratio with the phospholipid. Therefore, based on these general teachings of suitable amounts and ratios, it would have been obvious to one of ordinary skill in the art to manipulate the amounts of the phospholipids and the fatty acids in order to determine the optimal amount to include the formulations.

According to the Examiner, since the novelty and inventiveness of the compositions of the invention do not reside in specific content of ingredients, or ratios between them, these statements are not relevant to the compositions of the invention, which possess storage stability of at least 6, or at least 12, or at least 24 months. The prior art compositions which comprise PS do not exhibit such, or even near, storage stability.

Regarding the claimed storage stability, the Examiner states that Kiliaan et al. is silent, but Haynes et al. do teach that incorporation of lipid stabilizers such as sterols can improve storage stability. Therefore, based on that teaching and that the compositions of Kiliaan et al. teachings comprising the same claimed ingredients, there is a reasonable expectation that the storage stability would be the same as instantly

claimed.

The Examiner states that the burden of proof is shifted to the Applicant to show that the functional limitation is not possessed by the prior art. Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

As mentioned above, the use of sterols in Haynes et al. is intended to stabilize the liposome formed from the phospholipids in water, not to stabilize the PS. The stable liposomes protect the fish oil entrapped therein. In the composition of matter of the present invention no liposomes are formed. The relevance of Haynes to the present invention is unclear, and adding sterols to the compositions of Kiliaan, if any motivation existed which is denied, would not result in storage stable compositions of PS, because sterols do not stabilize PS, they stabilize liposomes.

The Examiner rejected Claims 2, 9-12, 19, 24-25, 30-31 and 33-34 under 35 U.S.C. 103(a) as being unpatentable over Hensley et al. in view of Haynes et al. (US Patent No. 5015483), for the reasons detailed in the Action.

The Examiner states that the instant application claims a composition comprising from about 1 to about 99% (w/w) phosphatidylserine, from about 1 to about 99% (w/w) other functional ingredients, from about 1 to about 99% (w/w) phosphatidylcholine, from about 1 to about 99% (w/w) phosphatidylethanolamine, from about 1 to about 99% (w/w) phosphatidylinositol, from about 1 to about 99% (w/w) Omega-3 source, from about 1 to about 99% (w/w) Omega-6 source and/or from about 1 to about 99% (w/w) sterol or sterol esters.

According to the Examiner, Hensley et al. is directed to composition for the rapid

delivery of bioactive compounds. Exemplified formulations comprise mixed membrane phospholipids, omega-6 oils, and glycerin. According to the Examiner, it is taught by this reference that the phosphomatrix is prepared by combining one or more phospholipids selected from the groups consisting of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol (examples). Amounts of the phospholipids exemplified are from 87-96%. Further according to the Examiner, it is taught that the forms of the composition can be that of an aerosol, a liquid or gel, the composition includes components such as fatty acids, oils or water (page 5, lines 21-31) and suitable oils include polyunsaturated oils and monounsaturated oils such as omega 3, omega 6 and DHA (column 2, lines 32-33).

The Examiner stated that while Hensley et al. teach that the phosphomatrix comprises one or more phospholipids selected from the group consisting of phosphatidylserine, phosphatidylinositol, phosphatidylcholine and phosphatidylethanolamine, they do not exemplify formulations comprising all four phospholipids. While Hensley et al. teach that omega-3 and omega-6 oils can be utilized, Hensley et al. do not exemplify formulations comprising both. Hensley et al. do not teach incorporating sterol or sterol esters. However, this deficiency is cured by Haynes et al. Haynes et al. teach liposome compositions for the stabilization of oxidizable substances. The compositions comprise phospholipids and omega-3 and omega-6 fatty acids (column 5, lines 39-41). It is taught that cholesterol is known to be a stabilizer of phospholipids (column 2, lines 51-55). It is taught that in compositions comprising phospholipids other lipids such as sterols and cholesterol can be added in order to reduce the permeability, strengthen the vesicle wall and generally improve the physical characteristics of a resulting liposome (column 10, lines 5-11). The amount utilized will vary but generally not exceed a 1:1 ratio with the selected phospholipid (column 10, lines 15-17).

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Hensley et al. and Haynes et al. and utilize phosphatidylserine, phosphatidylcholine,

phosphatidylethanolamine, and phosphatidylinositol. The Examiner contends that one of ordinary skill in the art would have been motivated to utilize all four phospholipids as Hensley et al. teach utilizing one or more of these four phospholipids. The Examiner contends that since there are only four different phospholipids to choose from, which represent a finite number of different phospholipids, it would have been obvious to one of ordinary skill in the art to utilize a combination of all four as they are all taught as being suitable for the same purpose. The Examiner contends that since they are all taught as being suitable for the same purpose, there is a reasonable expectation of success in utilizing combinations of the respective phospholipids.

Thus, according to the Examiner, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Henley et al. and Haynes et al. and utilize both omega-3 and omega-6 fatty acids. The Examiner contends that one of ordinary skill in the art would have been motivated to utilize both as Hensley et al. teach that the matrix can comprise fatty acids and only teach two different fatty acids to incorporate. Therefore, The Examiner contends that it would have been obvious to one of ordinary skill in the art to utilize one or both of the fatty acids into the matrix.

Further, the Examiner states that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Hensley et al. and Haynes et al. and utilize sterol in the composition. The Examiner contends that one of ordinary skill in the art would have been motivated to add a sterol in order to improve the stability of the lipids as taught by Haynes et al.

Applicant respectfully traverses. As explained above, Haynes et al. relates to the preparation of stable liposomes, to protect fish oil entrapped therein from oxidation. The sterol is added to the phospholipids, in water, and contributes to the physical stability of the resulting liposomes, not of the phospholipids (e.g. PS).

Hensley et al. discloses a drug delivery system, which comprises phospholipids. The phospholipids are used as a carrier that mimics the physical properties of nasal mucosa (phosphomatrix carrier), thus expected to increase the rate of permeation of the active principal. Also this document describes entrapment of active ingredients in liposomes (e.g. paragraph bridging pages 4 and 5).

Therefore, even if the teachings of Haynes and Hensley are combined, the result would not be storage-stable PS, as in the present application. Moreover, there would be no motivation to combine the teachings of these two documents, for the reasons detailed above, as they relate to completely different fields (one describes liposomes and the other phosphomatrix carrier) and address different technical problems.

It is therefore respectfully submitted that the invention is not obvious over Hensley et al. in view of Haynes et al.

The Examiner further commented that regarding the claimed amounts, it is taught that amounts of the phospholipids range from 87-96% and exemplified amounts of the fatty acid is 10 wt. %. Haynes et al. teach that the amount of sterol will generally not exceed a 1:1 ratio with the phospholipid. Therefore, based on these general teachings of suitable amounts and ratios the Examiner contends that it would have been obvious to one of ordinary skill in the art to manipulate the amounts of the phospholipids and the fatty acids in order to determine the optimal amount to include the formulations.

In view of the above arguments, it is respectfully submitted that the essence of the present invention does not reside in specific amounts, which only define specific embodiments, all of which are novel and inventive since, as argued above, define a unique, stable PS compositions in which no more than about 1 to about 5% of the PS are decomposed after a storage period of at least 6 months.

The Examiner further states that regarding the claimed storage stability, Hensley et al.



is silent. The Examiner contends that Haynes et al. does teach that incorporation of lipid stabilizers such as sterols can improve storage stability. Therefore, based on that teaching and that the compositions of Hensley et al. teachings compositions comprising the same claimed ingredients, the Examiner contends that there is a reasonable expectation that the storage stability would be the same as instantly claimed. The Examiner states, as above, that the burden of proof is shifted to the Applicant to show that the functional limitation is not possessed by the prior art. Applicant submits the same arguments as above, stressing that in the present invention no stabilizers are added to achieve the remarkable storage stability, and that the PS of the invention has an enhanced stability in comparison with commercial PS used at the time the present application was filed (described in the Annex).

The Examiner rejected Claims 2, 9-19, 21-22, 24-25, 30-35 under 35 U.S.C. 103(a) as being unpatentable over Haynes et al.

The Examiner states that the instant application claims a composition comprising from about 1 to about 99% (w/w) phosphatidylserine, from about 1 to about 99% (w/w) other functional ingredients, from about 1 to about 99% (w/w) phosphatidylcholine, from about 1 to about 99% (w/w) phosphatidyl-ethanolamine, from about 1 to about 99% (w/w) phosphatidylinositol, from about 1 to about 99% (w/w) Omega-3 source, from about 1 to about 99% (w/w) Omega-6 source and/or from about 1 to about 99% (w/w) sterol or sterol esters.

The Examiner further states that Haynes et al. is directed to liposome compositions for the stabilization of oxidizable substances, and that liposomes are prepared from a wide variety of lipid compounds including phospholipids. The Examiner contends that phospholipids are taught and exemplified include phosphatidylserine, phosphatidylinositol, phosphatidylcholine, phosphatidylethanolamine, cholesterol, etc. and mixtures thereof (claim 6 and column 7, lines 24-35), and fish oils and in particular omega-6 and omega-3 fatty acid fish oils are known to be beneficial in controlling the

cholesterol level in blood and in preventing thrombotic disturbances (column 5, lines 39-56). The disclosure is directed to a method of effectively stabilizing readily oxidizable lipids. The liposomes prepared provide more stable lipids (column 6, lines 67-68). The Examiner contends that it is taught that the liposomes which can be readily dispersed in an aqueous medium or in a lipid medium (column 7, lines 6-7). The Examiner contends that it is taught that liposomes can be added directly to food preparations containing a high fat content such as margarines (column 7, lines 40-42). The Examiner contends that it is taught that the liposomes have the distinct advantage of being quite stable and an effective stabilizing means for reactive and oxidizable lipophilic materials (column 9, lines 22-24). The Examiner contends that it is taught that cholesterol is known to be a stabilizer of phospholipids (column 2, lines 51-55), and that in compositions comprising phospholipids other lipids such as sterols and cholesterol can be added in order to reduce the permeability, strengthen the vesicle wall and generally improve the physical characteristics of a resulting liposome (column 10, lines 5-11). The amount utilized will vary but generally not exceed a 1:1 ratio with the selected phospholipid (column 10, lines 15-17). The Examiner contends that it is taught that the liposome may be solid at room temperature and fluid when consumed to increase the rate of release of the lipophilic component to provide proper taste and mouth feel (column 10, lines 58-62). The Examiner contends that it is taught that the margarine will typically comprise 70 to 80% hydrogenated and interesterified vegetable oil (column 12, lines 67-68). According to the disclosure the amount of fish oil content is between 3 and 5% (column 13, lines 5-9), and cholesterol is claimed in an amount of about 3 to 5% (claim 7). According to the disclosure exemplified amounts of phospholipid is 25% (example 1). The Examiner contends that it is taught that the liposomes can comprise additional additives such as vitamins, glycerol, preservatives, flavorants, antioxidants, etc. (column 11, lines 25-30).

The Examiner states that while Haynes et al. teach that the phospholipids utilized to form the liposome include phosphatidylserine, phosphatidylcholine, phosphatidylethanolamine, and phosphatidylinositol, Haynes et al. do not exemplify a formulation comprising all four phospholipids. While Haynes et al. teach that the

encapsulated material includes fish oil, which comprises omega-6 and omega-3 fatty acids, Haynes et al. do not exemplify a formulation wherein the liposome which is comprised of the four different phospholipids encapsulates this source of fatty acid. While Haynes et al. teach one embodiment includes dispersing the liposome in margarine, which comprises vegetable, Haynes et al. do not exemplify a liposome comprising the four phospholipids in margarine. While Haynes et al. teach the incorporation of sterols for increased stability, Haynes et al. do not exemplify a liposome comprising the four phospholipids with a sterol.

The Examiner therefore concludes that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to utilize all four phospholipids in the formation of the liposomes. The Examiner contends that one of ordinary skill in the art would have been motivated to utilize these phospholipids as Haynes et al. exemplify a formulation comprising one of the phospholipids and teach that the polar lipid bilayer can comprise at least one substance selected from a group which comprises the four phospholipids and mixtures of these phospholipids. The Examiner contends that since all of the phospholipids are taught as being utilized for the same purpose and are all taught as suitable, one of ordinary skill in the art would have a reasonable expectation of success in utilizing all four in the formation of a liposome to encapsulate fish oil. Further, The Examiner contends that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to utilize sterol in the composition. The Examiner contends that one of ordinary skill in the art would have been motivated to add a sterol in order to improve the stability of the lipids as taught by Haynes et al. The Examiner contends that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to encapsulate fish oil which comprises both omega-3 and omega-6 fatty acids. The Examiner contends that one of ordinary skill in the art would have been motivated to encapsulate fish oil as it is taught and exemplified by Haynes et al. as a material to be encapsulated in order to improve its stability and mask the taste.

The Examiner further concludes that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to utilizing additional ingredients such as vitamins and antioxidants in the liposomes. The Examiner contends that one of ordinary skill in the art would have been motivated to add these ingredients as they are taught by Haynes et al. as being suitable to include and it would have been obvious to one of ordinary skill in the art to add customary additives to the liposome formulations.

Applicant respectfully traverses, for all of the reasons detailed above. In particular, Haynes refer to stabilizing the physical structure of liposomes, of which the PS is a constituent, and it does not refer in any manner whatsoever to stabilization of compositions of matter of PS. With reference to the Examiner's observations regarding specific amounts, also these are not relevant, because the invention does not reside in any specific amounts, as explained above.

The Examiner further stated that regarding the claimed storage stability, Haynes et al. teach that incorporation of lipid stabilizers such as sterols can improve storage stability and indicates that their compositions are shelf-stable. However, Haynes et al. is silent as the length of stability. The Examiner contends that therefore, based on that teaching and that the compositions of Haynes et al. comprise the same claimed ingredients, there is a reasonable expectation that the storage stability would be the same as instantly claimed. The Examiner again stated that the burden of proof is shifted to the Applicant to show that the functional limitation is not possessed by the prior art, and that therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicant respectfully traverses, for all of the reasons detailed above. Specifically, while Haynes et al. deals with stable liposome composition the present invention describes stable PS composition. The liposome stability is due to the presence of sterol, and not to the PS itself.

## Double Patenting

The Examiner provisionally rejected claims on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims in several co-pending applications as identified in the Office Action. The Examiner contends that although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope. The double patenting rejections will be dealt with by appropriate Terminal Disclaimers that are currently in preparation.

In light of the foregoing remarks, this application should be in condition for allowance, and early passage of this case to issue is earnestly solicited. If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

It is respectfully requested that, if necessary to effect a timely response, this paper be considered as a Petition for an Extension of Time, time sufficient, to effect a timely response, and shortages in this or other fees, be charged, or any overpayment in fees be credited, to the Deposit Account of the undersigned, Account No. 500601 (Docket no. 7056-X08-020).

Respectfully submitted,

A handwritten signature in black ink that reads "Martin Fleit". The signature is written in a cursive, flowing style.

Martin Fleit, Reg. #16,900

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.Attachment: **ANNEX**